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Pseudomonas aeruginosa: a Survey of Resistance in 136 Hospitals in Spain

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We carried out a nationwide study with all of the isolates of *Pseudomonas aeruginosa* collected in a week in 136 hospitals in Spain. The data on 1,014 isolates included resistance to the following antimicrobials: piperacillin-tazobactam, 7%; meropenem, 8%; amikacin, 9%; tobramycin, 10%; piperacillin, 10%; ticarcillin, 13%; imipenem, 14%; ceftazidime, 15%; cefepime, 17%; ciprofloxacin, 23%; aztreonam, 23%; ofloxacin, 30%; gentamicin, 31%. The most frequent serotypes were O:1 (25.1%), O:4 (21.6%), and O:11 (11.3%).

Pseudomonas aeruginosa is a nosocomial pathogen responsible for infections in immunocompromised hosts. Most studies report the resistance of *P. aeruginosa* to antimicrobials in special units and special types of patients. However, data regarding the antimicrobial susceptibility of *P. aeruginosa* without a priori selection are scarce.

The changing and easy acquisition of resistance in *P. aeruginosa* requires rapid surveillance procedures to represent the whole reality of the situation at a given point in time. Here we report a recent national point prevalence study (1998) of all of the *P. aeruginosa* isolates collected during a whole week in 136 randomly selected hospitals that are representative of all of the types and sizes of public hospitals found throughout Spain.

All isolates were sent to the same reference laboratory for reidentification and susceptibility testing without duplication of strains from the same patient and sample. All isolates were accompanied by a uniform protocol which included the characteristics of the hospital of origin, the number of beds, the ward, the sites of isolation, and acquisition from outpatients or inpatients. Identities and MICs were determined by using MicroScan Neg Combo 1S panels (MicroScan, Baxter Diagnostics, Inc., West Sacramento, Calif.) and following the manufacturer's guidelines. Those isolates whose identification was inconclusive were subjected to reidentification by standard procedures (4). The antimicrobials and concentrations (micrograms per milliliter) tested were as follows: ticarcillin and piperacillin 16 and 64; piperacillin-tazobactam, 16/4 and 64/4; ceftazidime, cefepime, and aztreonam, 1 to 2 and 8 to 16); imipenem, 1 to 8; meropenem, 4 to 8, ciprofloxacin, 0.12 and 1 to 2; ofloxacin, 0.5 and 2 to 4; gentamicin and tobramycin, 4 to 8; amikacin, 8 to 16. Each panel was inoculated with an appropriate dilution of an exponential phase culture of a microorganism. Readings were performed after overnight incubation at 35°C. *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used daily as control strains. Breakpoints were applied following National Committee for Clinical Laboratory Standards (NCCLS) recommendations (6). When resistance rates were calculated, MIC in both the intermediate and resistant ranges, as defined by the NCCLS, were considered as nonsusceptible in this study. Serotyping was performed by a slide agglutination method using 17 monovalent *P. aeruginosa* antisera from the international antigenic typing scheme (7). Susceptibility data were compared by using a chi-square test.

A total of 1,014 isolates were studied. Data regarding antimicrobial resistance are summarized in Table 1. The most active antimicrobials (resistance in ≤15% of all isolates) were amikacin, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ticarcillin, and tobramycin. By contrast, gentamicin and ofloxacin were the least active antimicrobial agents, with percentages of resistance of 31 and 30%, respectively. A large proportion of isolates (30.5%) were obtained from outpatients and the highest resistance was observed, in general, among the nosocomial isolates (although the difference was only statistically significant for ceftazidime and carbapenems). Among isolates from outpatients (24.5%), resistance to quinolones was significantly higher than that to other antimicrobial agents ($P < 0.05$). For outpatient isolates, urine was the most common site of isolation (31%), significantly more common than lower respiratory tract ($P < 0.05$). In contrast for strains from inpatients, lower respiratory tract was the most common site of isolation, significantly more common than urine ($P < 0.05$). We found significant differences ($P < 0.05$) regarding resistance to the following antimicrobials under the following cir-

TABLE 1. In vitro activities of antimicrobial agents against *P. aeruginosa*

Antimicrobial agent	NCCLS breakpoint(s)[a] (μg/ml)	Range	% Resistance[b]
Amikacin	>16	<8–>16	9
Aztreonam	>8	<1–>16	23
Cefepime	>8	<1–>16	17
Ceftazidime	>8	<1–>16	15
Ciprofloxacin	>1	<0.12–>2	23
Gentamicin	>4	<4–>8	31
Imipenem	>4	<1–>8	14
Meropenem	>4	<4–>8	8
Ofloxacin	>2	<0.5–>4	30
Piperacillin-tazobactam	>64/4	<16–>64	7
Piperacillin	>64	<16–>64	10
Ticarcillin	>64	<16–>64	13
Tobramycin	>4	<4–>8	10

[a] Includes intermediate and resistant categories.
[b] Percentage of resistance (includes all nonsusceptible [intermediate and resistant] isolates).

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TABLE 2. Cross-resistance of *P. aeruginosa* isolates

Drug(s) to which isolates were resistant	No. of strains[b]	% Resistance[a] to:												
		AK	AZT	CPE	CAZ	CIP	GN	IMP	MER	OFL	P/T	PI	TI	TO
Amikacin	87		42	55	37	54	100	29	19	70	21	32	36	56
Aztreonam	229	16		60	52	43	50	26	23	56	30	41	52	21
Cefepime	168	29	82		72	49	68	30	29	62	42	54	62	34
Ceftazidime	150	21	79	80		43	59	31	27	50	46	63	60	35
Ciprofloxacin	231	20	42	36	28		61	26	14	100	13	22	28	30
Gentamicin	317	27	36	36	28	44		20	15	57	13	21	27	31
Imipenem	141	18	42	36	33	43	45		48	55	20	25	28	16
Meropenem	80	21	67	61	51	41	57	85		57	34	40	49	24
Ofloxacin	305	20	42	34	25	76	60	25	15		13	20	28	26
Piperacillin-tazobactam	74	24	93	93	92	40	55	38	35	54		100	93	27
Piperacillin	106	26	90	87	89	47	63	35	31	57	70		82	39
Ticarcillin	130	24	91	81	68	51	66	30	30	67	59	66		36
Tobramycin	101	48	47	57	52	69	96	22	19	80	20	38	46	

[a] Includes all nonsusceptible (intermediate and resistant) isolates. Abbreviations: AK, amikacin; AZT, aztreonam; CPE, cefepime; CAZ, ceftazidime; CIP, ciprofloxacin; GN, gentamicin; IMP, imipenem; MER, meropenem; OFL, ofloxacin; P/T, piperacillin-tazobactam; PI, piperacillin; TO, tobramicin.
[b] Numbers of nonsusceptible strains are shown; some strains were resistant to more than one drug.

cumstances: isolates from intensive care units were more resistant to aztreonam, cefepime, ceftazidime, imipenem, ticarcillin, piperacillin, and piperacillin-tazobactam than those from other clinical settings; isolates from inpatients were significantly most often resistant to ceftazidime, imipenem, and meropenem; and isolates from outpatients were more often resistant to ciprofloxacin than were nosocomial isolates.

P. aeruginosa was isolated in polymicrobial culture from 30% of the specimens (40% of those were from wounds or abscesses). Table 2 summarizes the cross-resistance of *P. aeruginosa* isolates to antimicrobial agents. The majority of meropenem-resistant isolates were also resistant to imipenem, and about one-half of these isolates and two-thirds of the imipenem-resistant isolates were susceptible to ceftazidime, piperacillin-tazobactam, and ciprofloxacin. About one half of the ceftazidime-resistant isolates (MIC, $\geq$16 μg/ml) were susceptible to piperacillin-tazobactam (MIC, $\leq$64/4 μg/ml), and around 70% were susceptible to imipenem and meropenem. All amikacin-nonsusceptible isolates (MIC, >16 μg/ml) were also resistant to gentamicin, but surprisingly, 44% were susceptible to tobramycin (MIC, $\leq$4 μg/ml). Seventy percent of the gentamicin-resistant isolates were susceptible to tobramycin and amikacin. More than two-thirds of the ciprofloxacin-resistant isolates were susceptible to ceftazidime, carbapenems, piperacillin-tazobactam, tobramycin, and amikacin.

The serotypes found were O:1 (25.1%), O:4 (21.6%), O:11 (11.3%), O:2 (8.3%), O:3 (7.1%), O:8 (6%), O:9 (3.2%), O:12 (2.8%), and others (14.6%).

Our study shows an inexpensive method to assess the situation of *P. aeruginosa* in a very large population without selecting types of patients and/or special situations. In a recent study, *P. aeruginosa* was the fourth most common nosocomial pathogen in the United States (5). To our surprise, in our study, a high percentage of *P. aeruginosa* isolates were obtained from outpatients and 24.5% of them were resistant to quinolones. This study was not specifically designed to address the definition of community-acquired infections according to Centers for Disease Control and Prevention criteria but points against *P. aeruginosa* as a potential pathogen in patients outside the hospital. The low percentage of susceptibility to ciprofloxacin may reflect the ubiquitous use of quinolones in the community.

This study demonstrates that β-lactams, despite having been in use for a longer time, have higher in vitro activity than quinolones. Recent studies in France and Italy (1, 2) showed similar results, although resistance percentages are lower in Spain, especially for ciprofloxacin (higher than 30% in France and Italy). Cross-resistance data indicate that a high number of isolates probably have resistance due to a combination of multiple unrelated resistance mechanisms.

The distribution of serotypes in Spain may have changed in recent years. A previous report obtained from 1980 to 1991 shows a different distribution (10). The main changes are the increase of serotypes O:4 and O:1 (from 8.7 to 14.4% and from 20.6 to 25.1%, respectively). Another important serotype, O:11, which is related to outbreaks and multi-drug resistance (3, 9), also accounts for an important percentage of the isolates found in our country, while serotype O:12, well known by its spread in all of Europe (8), accounts for a low percentage of the isolates found in Spain.

This study shows that periodical surveillance studies of this type, when resources are limited, provide very useful data on the overall situation in a country.

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